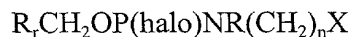


What is claimed is:

1. A compound of the formula



wherein

- 5 R is C₁-C₄ alkyl or -(CH₂)_nX;

n is 4 or 5;

X is an electrophilic group capable of being nucleophilically displaced from its bonded carbon atom;

halo is chloro, bromo or iodo; and

- 10 the group R_rCH₂- is a biologically labile ester forming group.

2. The compound of claim 1 wherein n is 4.

3. The compound of claim 1 wherein n is 5.

4. The compound of claim 1 wherein R is methyl.

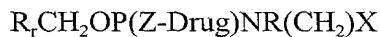
5. The compound of claim 1 wherein halo is chloro.

- 15 6. The compound of claim 1 wherein X is chloro or bromo.

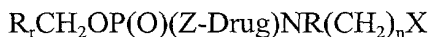
7. A method of preparing a phosphoramidate prodrug for enhanced intracellular delivery of a drug as phosphate ester or amide said method comprising the steps of reacting a hydroxy functional or amino functional drug compound (Drug-ZH) with a compound of the formula



under conditions conducive to the formation of an intermediate compound of the formula



and oxidizing that intermediate to form the phosphoramidate prodrug of the formula



in which formulas

R is C₁-C₄ alkyl or -(CH₂)_nX;

n is 4 or 5;

Z is O or N;

5 X is an electrophilic group capable of being nucleophilically displaced from its bonded carbon atom;

halo is chloro, bromo or iodo; and

the group R_1CH_2- is a biologically labile ester forming group.

8. The method of claim 7 wherein Drug-ZH is an amino acid, or a
10 biologically active peptide or peptidomimetic.

9. The method of claim 8 wherein Drug-ZH is a peptidomimetic of the formula



wherein Z is O or N;

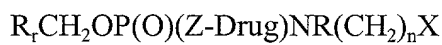
q and k are independently 1 or 0; and

B is H, amino, protected amino or C₁-C₄ alkanoylamino.

10. The method of claim 7 wherein Drug-ZH is a biologically active nucleotide analog.

11. A phosphoramidate compound formed from a hydroxy functional or amino functional drug compound of the general formula Drug-ZH said prodrug being a compound of the formula

-64-



wherein

R is C₁-C₄ alkyl or -(CH₂)_nX;

n is 4 or 5;

5 Z is O or N;

X is an electrophilic group capable of being nucleophilically displaced from its bonded carbon atom;

halo is chloro, bromo or iodo; and

the group R₁CH₂- is a biologically labile ester forming group.

10 12. The prodrug of claim 11 wherein the drug is an amino acid, or a biologically active peptide or peptidomimetic.

13. The method of claim 12 wherein Drug-ZH is a peptidomimetic of the formula



wherein Z is O or N;

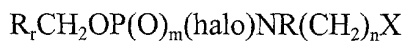
q and k are independently 1 or 0; and

20 B is H, amino, protected amino or C₁-C₄ alkanoylamino.

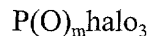
14. The prodrug of claim 11 wherein the drug is a biologically active nucleotide analog.

15. A method of preparing a compound of the formula

-65-



comprising the steps of reacting a compound of the formula



with 1) an alcohol of the formula R_1CH_2OH and 2) an amine of the formula

5 $HNR(CH_2)_nX$, each in the presence of an acid scavenger,

wherein in the above formulas

m is 0 or 1;

R is C_1 - C_4 alkyl or $-(CH_2)_nX$;

n is 4 or 5;

10 X is an electrophilic group capable of being nucleophilically displaced from its bonded carbon atom;

$halo$ is chloro, bromo or iodo; and

the group R_1CH_2- is a biologically labile ester forming group.

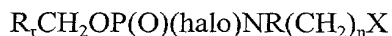
16. A method of preparing a phosphoramidate prodrug of the formula

15 $R_1CH_2OP(O)(Z-Drug)NR(CH_2)_nX$

for enhanced intracellular delivery of a compound of the general formula $Drug-ZPO_3$

said method comprising the steps of reacting a hydroxy functional amino functional drug

compound of the formula $Drug-ZH$ with a compound of the formula



20 under conditions conducive to the formation of the prodrug

wherein in the above formulas

R is C_1 - C alkyl or $-(CH_2)_nX$;

n is 4 or 5;

Z is O or N;

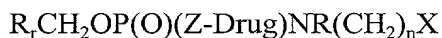
-66-

X is an electrophilic group capable of being nucleophilically displaced from its bonded carbon atom;

halo is chloro, bromo or iodo; and

the group R_fCH_2- is a biologically labile ester forming group.

- 5 17. A pharmaceutical composition comprising
a phosphoramidate compound formed from a hydroxy functional or amino functional drug compound of the general formula Drug-ZH said prodrug being a compound of the formula



- 10 wherein

R is C_1-C_4 alkyl or $-(CH_2)_nX$;

n is 4 or 5;

Z is O or N;

X is an electrophilic group capable of being nucleophilically displaced from its bonded carbon atom;

halo is chloro, bromo or iodo;

the group R_fCH_2- is a biologically labile ester forming group; and

a pharmaceutically acceptable carrier therefor.

- 15 18. The pharmaceutical compound of claim 17 wherein Drug-ZH is an amino acid or a biologically active peptide or peptidomimetic.

19. The pharmaceutical composition of claim 18 wherein Drug-ZH is a peptidomimetic of the formula



5

wherein Z is O or N;

q and k are independently 1 or 0; and

B is H, amino, protected amino or C₁-C₄ alkanoylamino.

20. The pharmaceutical composition of claim 17 wherein Drug-ZH is a nucleotide analog.

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